REMARKS

This is in response to the outstanding Official Action. Applicants have complied with the recommended change to the Abstract, and appropriate amendment is made herein. Applicants traverse the remaining rejections. Among other things, the instant claims have been amended to mare particularly point and distinctly claim that which applicants believe to be their invention. Any and all claim amendments and cancellations presented herein are made without prejudice or disclaimer.

35 USC 101

The claims have been amended to expressly state that the bone model is an *in vitro* model. As such, it would have been clear to one of skill in the art that the creation and use of the model requires intervention and/or the "hand of man." Thus, the invention, as claimed, distinguishes over a remodeling bone system naturally occurring in a mammal.

Further, the claimed model requires three elements: a matrix, osteoclasts, and osteoblasts. The claims recite that the osteoclasts have been placed on the matrix, and osteoblasts have been placed on the osteoclasts. In the context of an *in vitro* model, one skilled in the art would have appreciated that the "placing" of the obsteoblasts and osteoclasts are performed by the hand of man. Thus, the claimed invention is different from a naturally occurring remodeling bone system.

Applicants respectfully request further examination, and reconsideration and withdrawal of the rejection.

35 USC 112

Applicants amend claims 2 and 20 to overcome the various rejections under Section 112. The claims as amended now more particularly point out and distinctly claim the invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Prior Art Rejections

Novelty

USPN 6,152,964 (Van Blitterswijk). The cited example of the '964 reference is directed to a study to examine the effect of osteoblast derived factors on osteoclastic resorption. Among other things, the study describes culturing osteoblasts on calcium phosphate substrata for 18 days, followed by the addition of a culture of young rat osteoclasts. The reference fails to disclose a co-culture of osteoblasts and osteoclasts, and thus does not anticipate the claimed invention.

The '964 reference also fails to disclose the use of osteoblasts at confluence on the support. Thus, the reference fails to anticipate the instant claims.

Another distinction is that the '964 reference relates to the *in vitro* production of bone tissue to be used as implant material, e.g., in reconstructive surgery. *See, e.g.,* Abstract ("The produced matrix can be used for joint prostheses, maxillofacial implants, special surgery devices, or bone fillers."). Despite the fact that the '964 reference described an *in vitro* system including bone cells such as osteoblasts and osteoclasts, one skilled in the art would have appreciated that there is no link between the objectives of those workers and the instant subject matter. The instant claims are directed to an *in vitro* system that can be used as an *in vitro* diagnostic

test for osteoclast transmigration. The '964 reference neither teaches nor suggests such a use. Thus, the '964 reference neither teaches nor suggests the claimed invention.

Kikuchi et al. discloses a substrate composed of collagen and hydroxyapatite as the best substrate to mimic a bone surface. The object is to incorporate the substrate *in vivo* (p.1706, col 2 - p. 1707, col 3; and p. 1709, col. 1). The reference fails to disclose an *in-vitro* system comprising a mineralized matrix, a layer and/or nodule of osteoblasts at confluence on said matrix, and osteoclasts disposed on said layer and/or nodule. Thus the instant claims are novel over the Kikuchi reference.

Obviousness

Shibutani et al. discloses the use of glass slides coated with an apatite-collagen complex for measurement of osteoclastic resorption activity. The reference includes a description of a system of seeding osteoclasts on a glass slide coated with apatite-collagen, and asserts that the osteoclasts could resorb the apatite particles. As acknowledged in the Official Action, however, this does not disclose or suggest that a layer and/or nodule of osteoblasts at confluence could be seeded on such a glass slide. Further, the reference does not teach or suggest the seeding of osteoclasts on a layer of osteoblasts at confluence.

Chambers does not cure the deficiencies of Shibutani. First, Chambers is not directed to a bone model system, but rather explores the mechanism by which osteoclasts effect bone resorption.

Among other things, it is asserted that Chambers (1985) shows that osteoblasts are capable of osteoid destruction. However, the reference does not

make that statement. Rather, Chambers states: "We have found that both resident bone cells and neonatal calvarial cells are able to digest osteoid *in vitro*. Amongst the cell types present in our cultures, *cells of the osteoblastic lineage may be responsible*...." Chambers, p. 163. The reference also states that the role of osteoblasts in osteoid destructions is merely "suggested by the hormone-dependent nature of the process." *Id.* Thus, Chambers merely speculate that osteoblasts *might* play a role in osteoid destruction. Subsequently, however, the reference itself acknowledges that "there was no evidence that such cells were capable of resorption of bone mineral...." *Id.*

In fact, the speculation proved erroneous. Subsequent research has shown that osteoblasts do not participate in osteoid destruction, and that showing has come to be generally accepted within the art. One skilled in the art would know that osteoblasts are not capable of osteoid destruction. *See, e.g.,* Teitelbaum, S.L., "Osteoclasts; culprits in inflammatory osteolysis", Arthritis Res. Ther. 2006;8(1):201, Epub 2005 Nov 29, Abstract ("The osteoclast, which is a member of the monocyte/macrophage family, is the *exclusive bone resorptive cell*, and its differentiation and activation are under the aegis of a variety of cytokines." emphasis added); s*ee also,* Karsenty, G., "The Genetic Transformation of Bone Biology", Genes & Development 13:3037-3051, at 3037 (1999), Cold Spring Harbor Laboratory Press; and Komori, T., "Regulation of Osteoblast Differentiation by Transcription Factors", J. Cell. Biochem., 99:1233-1239 (2006).

Chambers likewise does not disclose an *in vitro* system as a bone system model as in claim 1. Nor does Chambers teach or suggest that osteoclasts seeded on a confluent layer of osteoblasts are capable of making their way through the joint

population of osteoblasts so as to form a bone system model as claimed. As such, the reference is unrelated to the instant models.

Rovira et al. likewise fails to cure the deficiencies of Shibutani, alone or in combination with Chambers. Rovira describes new biomaterial allegedly suitable as substitute for bone tissue for purposes of developing effective orthopaedic implants. The reference does not describe a bone system model for diagnosing or assaying therapies for bone related maladies as is claimed here.

Rovira instead describes a biomaterial based on calcium phosphate particles linked to an artificial connective matrix, elastin-solubilized peptides (ESP) associated with type I and type II collagens. The reference is said to provide an evaluation of the capacity of the biomaterial as a substrate for the proliferation of human osteoblasts.

Rovira fails to teach or suggest a system comprising a matrix, a layer and/or nodule of osteoblasts at confluence on said matrix, and osteoclasts deposited on said layer and/or nodule. Nor does the reference teach or suggest how the biomaterial that is disclosed could have been used as a bone system model.

Further, Rovira does not disclose an *in vitro* system as defined in claim 1, nor does it teach or suggest that osteoclasts seeded on a confluent layer of osteoblasts are capable of making their way through the joint population of osteoblasts.

Claim 20 has been rejected over Shibutani, Chambers, and Rovira, as combined above, and further in view of Traianedes. It is acknowledged that Shibutani, Chambers, and Rovira fail to disclose or suggest induction of rheumatoid arthritis in the bone system model, but that Traianedes provides that teaching.

Applicants traverse the rejection, and urge, as above, that Shibutani, Chambers and Rovira all fail to teach or suggest the subject matter of claims 1-4. The combination of those references with Traianedes fails to cure the deficiencies of those references with regard to claims 1-4, and so it likewise fails to teach or suggest the subject matter of claim 20.

Traianedes describes an effect of the leukotrienes and other metabolites on osteoblast function. Their data includes osteoblast cell cultures and organ culture. No co-culture model is used, and the paper focuses only on osteoblast (OB) function. The authors reference rheumatoid arthritis because leukotrienes are known to be pro-inflammatory molecules, and therefore are implicated in rheumatoid arthritis (RA). The instant model, however, includes layers of OB and addition of OC to test their capacity to transmigrate. Traianedes does not present any data on that particular OC property. The instant disclosure and claimed invention uses the disclosed transmigration test to evaluate the effect of drugs that can be used in RA, or in used cells extracted from RA mouse models (+/-) drugs.

Claim 17 has been rejected over Shibutani, Chambers, and Rovira, as combined above, and further in view of Rodan. It is acknowledged that Shibutani, Chambers, and Rovira fail to disclose or suggest the use of the claimed system for testing a substance, but argues that Rodan provides that teaching.

Applicants traverse the rejection, and urge, as above, that Shibutani, Chambers and Rovira all fail to teach or suggest the subject matter of claims 1-4. The combination of those references with Rodan fails to cure the deficiencies of those references with regard to claims 1-4, and so it likewise fails to teach or suggest the subject matter of claim 17.

Among other things, Rodan discloses an assay involving culturing an osteoclast-enriched population with Vitamin D3 or a biologically active derivative thereof, with a test substance, and measuring the amount of bone resorption.

Rodan does not disclose an example of assaying compounds on a population as recited in the instant claims, e.g., mineralized matrix, layers or nodules of osteoblasts, and a layer of osteoclasts.

Further Rodan does not disclose or suggest the system of claim 1, or how to adapt it to test chemical molecules on osteoblasts and osteoclasts at the same time.

Claim 6 has been rejected over Shibutani, Chambers, and Rovira, as combined above, and further in view of Choi et al. It is acknowledged that Shibutani, Chambers, and Rovira fail to disclose or suggest the use of genetically modified osteoclasts in the claimed system, but argues that Choi provides that teaching.

Applicants traverse the rejection, and urge, as above, that Shibutani, Chambers and Rovira all fail to teach or suggest the subject matter of claims 1-4. The combination of those references with Choi fails to cure the deficiencies of those references with regard to claims 1-4, and so it likewise fails to teach or suggest the subject matter of claim 6.

Choi discloses methods and compositions that modulate the activity of cells such as osteoblast cells (see abstract). Choi discloses a nucleic acid molecule called OSCAR identified in osteoclast cells, and describes means for studying its activity. Choi does not disclose or suggest any system as defined in claim 1. Moreover, this document does not suggest the use of a genetically modified cell in the system of the present invention.

Claim 5 has been rejected over Shibutani, Chambers, and Rovira, as combined above, and further in view of Sun et al. It is acknowledged that Shibutani, Chambers, and Rovira fail to disclose or suggest the use of osteoclasts to osteoblasts in the ratio of 1/10 to 1/25, but argues that Sun provides that teaching.

Applicants traverse the rejection, and urge, as above, that Shibutani, Chambers and Rovira all fail to teach or suggest the subject matter of claims 1-4. The combination of those references with Sun fails to cure the deficiencies of those references with regard to claims 1-4, and so it likewise fails to teach or suggest the subject matter of claim 5.

Sun discloses a study on the effect of hydoxyapatite size on osteoblasts and osteoclasts. Sun discloses the effect of hydoxyapatite size on the ratio of osteoblasts/osteoclasts. Sun does not disclose or suggest a system as recited in claim 1.

Finally, applicants invite the examiner's attention to the fact that none of the cited references discloses or suggests that osteoclasts, which are ten times the size of osteoblasts, could or would be expected to migrate through the joint population of osteoblasts to effect resorption activity directly on the bone matrix. Without such an understanding or expectation, there would have been no reasoned basis for constructing or employing the system as claimed. Therefore the subject-matter of the claim set is not obvious over the cited references.

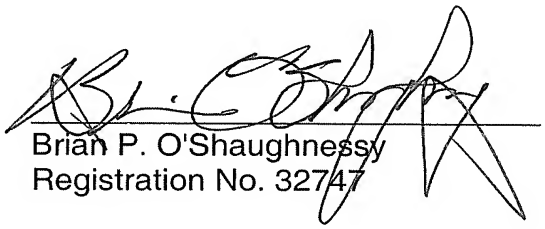
Conclusion

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to call Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: May 13, 2009

By: 

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